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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,774	06/19/2000	Bernd Groner	4-19924C/C1C1	4601

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/596,774	GRONER ET AL.	
	Examin r	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this c mmunicati n appears n the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1,8,12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-7,9-11,13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *23* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: notice to comply

DETAILED ACTION

After review and reconsideration, the finality of the Office action of Paper No. 14 is withdrawn. Claims 1-15 are pending. Claims 1, 8, 12 and 14. remain withdrawn from consideration. Claims 2-7, 9-11, 13 and 15 are under consideration.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper, see page 5, lines 4-6. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The disclosure is objected to because of the following informalities: the cross reference to related application contains a typographic error in reference to 08/703,048 which should be 08/793,048 and a blank after the phrase "filed September 23, 1998, now____".

Appropriate correction is required.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) on page 5, line 18, page 17, lines 28 and 30, and Figure 1 "EIKALEISNS" and "GLDFLEDPKlCYLLDG". However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claims 2 and 10 are objected to because of the following informalities: Claim 2 recites the typographical error of "comprising form about" . Claim 10 is object to for being dependent on non-elected claim 1. Also, claim 10 reads "culturing a host cell of containing DNA encoding said protein". Appropriate correction is required.

Claim 3 is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. When the claims of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims of the patent application. SEQ ID NO:4 is the antigen binding domain of FRP5. Appropriate correction is required.

Claims 2-7, 9-11, 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of claims 2 and 5 cannot be determined because the difference between a "functional" zeta chain of a TCR and "the" zeta chain of the TCR is not set forth in the specification.

Claim 2 is rendered vague and indefinite in the recitation of "derivable" from an anti-ErbB2 antibody" and "derivable" from the T-cell receptor. The recitation of "derivable from" rather than "derived from" indicates that the claimed antigen binding domains and zeta chains are not absolutely limited to the antigen binding domains of the anti-Erb2 antibody or the zeta chain of the TCR, as "derivable from" can read on structural alterations of said antigen binding domain and zeta chain.

The recitation of FRP5 as the only means of identifying the DNA encoding said protein renders claim 3 indefinite. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the mAb or hybridoma is required, because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

Claim 5 is rendered vague and indefinite as the claim does not state the origin of the transmembrane and cytoplasmic domains.

Claims 9 and 10 are vague and indefinite in the recitation "introducing into said CTL a DAN according to claim 2" and "production of a protein according to claim 1" . Claims 1 and 2

are product claims, therefore the methods of claims 9 and 10 cannot be carried out according to claims 2 and 1, respectively. Amendment of claim 9 to recite "the DNA of claim 2" and amendment of claim 10 to recite the "protein encoded by the DNA of claim 2" would overcome this rejection.

Claim 10 lacks an active method step which links the expression of the DNA encoding the protein, with the production of the protein as stated as the method objective in the pre-amble.

The recitation of "use of a host cell" in claim 13 is vague and indefinite because the claim fails to set forth any active, positive steps that define the claimed method.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2-7, 11, 13 and 15 rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. When given the broadest reasonable interpretation the claims can be construed as reading on a patient having been administered the host cells, vectors Amendment of the claims to incorporate the limitation of "isolated" in reference to the claimed DNAs, host cells, CTL and vector. .

Claim 13 is further rejected under 35 U.S.C. § 101 because it is lacking the format of a proper process claim. See MPEP 2173.05(q).

Claims 2-7, 9-11, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capon et al (WO 92/10591, reference AC of the IDS filed Sep 19, 2000) in view of Wels et al (EP 502,812, reference AP of the IDS filed Sep 19, 2000) and Huse et al (Science, 1989, Vol. 246, pp. 1275-1281) . Claim 2 is drawn to a DNA encoding a bifunctional protein, wherein said protein comprises: (i) an antigen-binding domain derivable from an anti-ErbB2 antibody; (ii) a hinge region comprising from about 40 to about 200 amino acids, and (iii) a functional zeta chain derivable for the T-cell antigen receptor. Claim 3 embodies the DNA of claim 2 wherein

the antigen-binding domain is derivable from FRP5. Claim 4 embodies the DNA of claim 2 wherein the hinge region is an immunoglobulin-hinge region.

Claim 5 embodies the DNA of claim 2 wherein the functional zeta chain comprises the transmembrane and cytoplasmic domain. Claim 6 is drawn to a host cell expressing the DNA of claim 2. Claim 7 embodies the host cell of claim 6 wherein said host cell is a cytotoxic lymphocyte. Claim 11 is drawn to a composition comprising the host cell of claim 6. Claim 15 is drawn to a vector comprising the DNA of claim 2.

Claim 9 is drawn to a process of endowing a CTL with a MHC-independent and unrestricted tumor cell specificity comprising introducing the DNA of claim 2 into a CTL.

Claim 10 is drawn to a method for producing the protein encoded by the DNA of claim 2 comprising culturing a host cell comprising the DNA encoding said protein under conditions which allow the expression of a DNA encoding said protein.

Capon et al teach the DNA encoding a chimeric protein comprising and extracellular domain capable of binding to a ligand and transmembrane domain and a cytoplasmic domain capable of activating a signaling pathway. Capon et al teach the zeta chain of the T-cell receptor as the cytoplasmic domain (page 5, lines 16-17 and claim 11). Capon et al teach that the transmembrane domain may be the domain of the protein contributing the cytoplasmic portion (page 6, lines 26-27, and claim 7), thus fulfilling the specific embodiment of claim 5 drawn to the transmembrane and cytoplasmic domains of the zeta chain. Capon et al teach that the extracellular domain may be part of a protein which is monomeric, homodimeric, heterodimeic or associated with a larger number of proteins and in particular may consist of an Ig heavy chain which may in turn be covalently associated with the Ig light chain by virtue of the presence of CH1 and hinge regions or may become covalently associated with other Ig heavy/light chain complexes by virtue of the presence of hinge, CH2 and CH3 domains (page 7, lines 18-27, and claims 3 ,12 and 17-19). Claim 47 of Capon et al states that a binding site is defined by the mammalian cell expressing the extracellular domain bound to a second protein, which is consistent with the association of the Ig heavy chain with the Ig light chain by means of the hinge region. It is recognized that the binding site of an antibody is formed by association of the CDR from the light chain and the CDR from the heavy chain. Capon et al teach that for the antibody receptor, ligands of interest include the Her-2 protein which is amplified in human

breast and ovarian carcinomas (page 16, lines 16-21). Capon et al teach an expression cassette comprising the DNA encoding the chimeric protein (claim 8) and a cytotoxic T-lymphocyte as a host cell (claims 24 and 25), thus fulfilling the limitation of claim 7. Capon et al teach the cytotoxic lymphocyte comprising the chimeric protein wherein said cell is substantially free of Class I or Class II MHC (claim 26) and a method for activating cells comprising contacting said cells with a ligand which binds to said extracellular domain and transduces a signal to said cytoplasmic domain , thus fulfilling the specific embodiment of claim 9. Capon et al teach a method of producing the chimeric protein by means of transformation and culturing of a host cell (page 12, lines 16-19 and page 13, line 23 to page 14, line 15) fulfilling the limitations of claim 10.

Capon et al, although suggesting a target ligand of Her-2, does not specifically teach DNA encoding a chimeric protein wherein the extracellular portion comprises an antigen-binding domain derivable from an anti-ErbB2 antibody.

Wels et al teach the coda encoding chimeric proteins comprising an antigen-biding domain derivable for an anti-ErbB2 antibody, wherein the portion of the DNA encoding the antigen-binding domain comprises the scFv of FRP5 which is taught by Wels et al to be SEQ ID NO:4 (page 31). Wels et al teach that SEQ ID NO:1 was the variable heavy chain of the anti-ErbB2 antibody and SEQ ID NO:2 was the variable light chain of said antibody (page 20, lines 31-32).

Huse et al teach that monovalent Fab fragments have less affinity for antigen than bivalent antibodies (page 1280, second column, lines 3-5 of the second full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the DNA encoding the light chain variable region and the DNA encoding the heavy chain variable region as the extracellular domains in the method taught by Capon et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Wels et al on the ability of the recombinant fusion proteins comprising said DNA to bind exhibit the characteristic of the anti-ErbB2 antibody in binding to target antigen, and the teachings of Capon et al who suggest that the extracellular domain of the fusion proteins be a ligand for the Her-2 protein which is synonymous with

ErbB2. One of skill in the art would be motivated to express the chimeric protein comprising the cytoplasmic domain and the transmembrane domain of the zeta chain of the T-cell receptor fused to the single chain antibody of the anti-ErbB2 antibody in addition to an immunoglobulin hinge region so as expression of the chimeric protein in lymphocytes allowed for the formation of dimers of said chimeric proteins by virtue of the cysteine residues within the transmembrane region of the zeta chain, known to comprise a cysteine residue capable of disulfide bonding (Capon et al, page 7, lines 5-7) and by virtue of the hinge region of the antibody (Capon et al, page 7, lines 21-27). One of skill in the art would be motivated to form extracellular regions comprising dimers of the single chained antibody because the resulting dimeric protein would be bivalent and be expected to have a greater affinity for antigen than the monomeric single chained recombinant antibody.

The rejection of claims 2-7, 9-11, 13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Stancovski et al, (Journal of Immunology, 1993, Vol. 11, pp. 6577-6582) in view of Brocker et al (Eur. J. Immunology, 1993, Vol. 23, pp. 1435-1439, reference AA of the IDS filed 9/22/00) and Horgan et al (Journal of Immunology, 1993, Vol. 150, pp. 5400-5407) is withdrawn in light of applicants arguments.

All other rejections and objections as set forth in Paper No. 14 are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

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8/27/03